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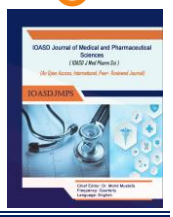

The Emerging Role of Nanoparticles in MRI as Targeted Contrast Agents

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ABSTRACT

Magnetic resonance imaging (MRI) is a widely accepted diagnostic technique that is especially well-known for its high-resolution imaging, superior soft tissue contrast, and non-ionizing radiation characteristics. However, the use of contrast agents becomes important to maximise MRI's sensitivity and specificity towards specific disorders. In order to increase image quality and diagnostic precision, recent advancements have concentrated on MRI contrast agents. Nanoparticle-based MRI contrast agents have emerged as a promising alternative to conventional agents, offering improved contrast enhancement, prolonged circulation time, and the potential for targeted imaging. However, a variety of contrast agents are available, including dual contrast agents, manganese-based nanoparticles (MnO), and iron-oxide-based nanoparticles (SPIONS). It helps in surface functionalization and target imaging techniques that enable biocompatibility, reduce immune clearance, and allow for the attachment of targeting ligands. The functions of nanoparticles in MRI-guided treatments, such as targeted drug administration, radiation therapy, photodynamic therapy, immunity-boosting therapy, and gene therapy. This review highlights recent developments, challenges, and future prospects in the field of nanoparticle-based MRI contrast agents, with an emphasis on their clinical translational potential.

Keywords: Nanoparticles in MRI, high-resolution imaging, superior soft tissue contrast, and non-ionizing radiation characteristics.

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1. INTRODUCTION

Magnetic Resonance imaging (MRI) is a non-invasive imaging modality that uses high magnetic fields and Radio frequency (RF) pulse to form the images of internal organs and soft tissue with high resolution. Paul Lauterbur and his associates were the first to demonstrate the feasibility of using paramagnetic contrast agents to improve tissue enhancement on MRI (Edelman, 2014). The majority of these agents are either paramagnetic ion complexes or superparamagnetic magnetite particles and contain lanthanide elements such as gadolinium (Gd3+) or transition metal manganese (Mn2+).Gadolinium-based chelates particularly Gadolinium-DTPA, have been the clinically used in 1998as intravenous contrast agent for MR imaging (Iyad et al., 2023). These contrast agents are categorised as either T1 (positive) or T2 (negative). T1contrast agents reduceT1 relaxation time, leading to increased signa (brightness) on T1-weighted images and also called as positive-contrast agents. These are clinically used in the examination of vessels, tumors, inflammation, or disrupted blood-brain barrier areas on T1-W images (Zhang et al., 2025). Commonly used T1-positive agents are Gadolinium-based contrast agents (GBCAs) such as Gd-DTPA (Magnevist), Gadobutrol (Gadovist), Gd-BOPTA and Manganese-based agent include Mangafodipir trisodium. Similarly, T2 contrast agent reduces the T2 relaxation time, causing the loss of signal intensity (darkening) on T2-weighted images and also known as the negative contrast agent. Used to

supress the signal intensity in certain tissues. Commonly used agents are Iron oxide-based nanoparticles include superparamagnetic iron oxide (SPIO) and ultrasmall SPIO (USPIO) such as Ferumoxides (Feridex), Ferumoxtran (Rahman, 2023). However, radiologists prefer T1 positive contrast to easily detect internal bleeding and air tissue borders and provides good image enhancement but there are certain limitations also present such as their non-specific distribution that requires high concentrations for effective imaging, their low relaxing efficiency at low dosages, and the potential for adverse effects, such as nephrogenic systemic fibrosis in patients with severe kidney failure (Siddique & Chow, 2020). As a result, there is an urgent need for MRI contrast materials with enhanced targeting capabilities, safety, and efficiency. Nanotechnology has played an important role to find out a better contrast agent. It provided an innovative solution as nano-particle based contrast agent. Superparamagnetic iron oxide nanoparticles are an excellent alternative to Gd. Nano-materials coated with biocompatible chemicals can significantly increase the safety and imaging effectiveness of MRI contrast agents. Additionally, localized therapy and targeted drug administration can be made easier by functionalized nanomaterials and combines therapeutic and diagnostic capabilities (Hsu et al., 2023).

In addition to enabling real-time treatment response monitoring, this strategy shows potential for cutting-edge methods including photodynamic therapy, hyperthermia therapy. Studies have demonstrated that gold nanoparticles can be employed for both simultaneous photothermal therapy of tumors and improved imaging, demonstrating the agents' dual utility in cancer treatment. This paper aims to provide current information about the nanoparticle as contrast agent along with its types and clinical applications.

2. Types of nanoparticles-based contrast agent

2.1 SPIONs nanoparticle-based

SPIONs are composed of iron oxide (Fe3O4 or Fe2O3) and coated biocompatible substances such as PEG (Polyethylene Glycol) and silica. These particles show superparamagnetism only in presence of external magnetic field, if the external field turn off these particles will not show the superparamagnetic property (Vangijzegem et al., 2023). They can produce local field inhomogeneity in the tissue of interest and effectively reduce transverse relaxation time (T2 shorting), which lead to hypointense signal (darker) on T2 weighted images. They increase the signal intensity in T1 weighted sequences which lead to enhancement in different tissues and use vascular imaging, cell tracking, lymph node imaging, inflammatory imaging, infection imaging, and tumor imaging (Topriceanu et al., 2022). SPION also play a crucial role in drug delivery, magnetic hyperthermia, and the identification of ferroptosis, a condition in which significant iron accumulate in cells and lead to cell death (Nieciecka et al., 2021).

2.2 MnO nanoparticle-based

MnO nanoparticles are effective T1 CAs by reducing the T1 relaxation time of water protons leading to brighter signals on the T1 - weighted image. The reticuloendothelial system may retain MnO nanoparticles, which are then concentrated in the spleen and liver, leading to Mn2+ toxicitym (Mounika et al., 2023). Chevallier and associates bonded pegylated bis-phosphonate dendrons (PDns) to the surface of MnO to reduce its toxicity in vivo. This significantly enhanced colloidal stability, relaxation performance, and quick excretion ability (Cai et al., 2019). Surface coating, which includes phospholipid modification, PEG, silica coating. This coating enables prolonged circulation, allowing more contrast enhancement in the desired area. Many researches have favoured PEG-modified MnO (Shi et al., 2021). They can be used in various applications, including tumor detection and diagnosis, and can be combined with other therapies like chemotherapy, radiotherapy, photothermal therapy, and photodynamic therapy (Zhao et al., 2024).

2.3 Dual-Mode nanoparticle-based

Dual-mode contrast agents are an emerging class of MRI nanoparticles designed to combine both T1 (positive) and T2 (negative) contrast effects. These agents use to overcome the limitations of using either T1 or T2 agents alone by providing complementary imaging data-T1 contrast offers high signal intensity and anatomical detail, while T2 contrast highlights pathophysiological changes through signal loss (Geraldes, 2024). superparamagnetic iron oxide nanoparticles (SPIONs) can be doped or conjugated with gadolinium (Gd^{3+}) or manganese (Mn^{2+}) to simultaneously shorten both T1 and T2 relaxation times. Surface modifications like PEGylation improve biocompatibility and circulation time, while targeting ligands such as antibodies or peptides can direct the agent to specific tissues or tumors. Dual-mode agents are particularly useful in molecular imaging, where precise localization and characterization of lesions are essential (Zou et al., 2024).

3. Recent advances in nanoparticles as MRI contrast agents

Chemotherapy and radiation therapy are most commonly methods for cancer treatment as shown in **Figure 1**. However, their non-specificity can result in significant collateral damage. Due to lack of selectivity, chemotherapeutic causes serious damage to both the targeted cancer cells and healthy cells (Bhat et al., 2024). Similarly, radiation used in radiotherapy can affect organs in close proximity because it produces oxygen-free radicals (Joshi et al., 2024). In order to address these issues, advances in nanotechnology and molecular imaging have produced nano-agents with both diagnostic and therapeutic capabilities. These nano-agents are being used in a variety of treatments, such as MRI-guided therapies, gene therapy, immunotherapy, photodynamic therapy, radiation therapy, targeted medication delivery,

and hyperthermia therapy. They provide a way for more personalized and successful cancer treatment plans (Akram et al., 2025; Gavas et al., 2021).

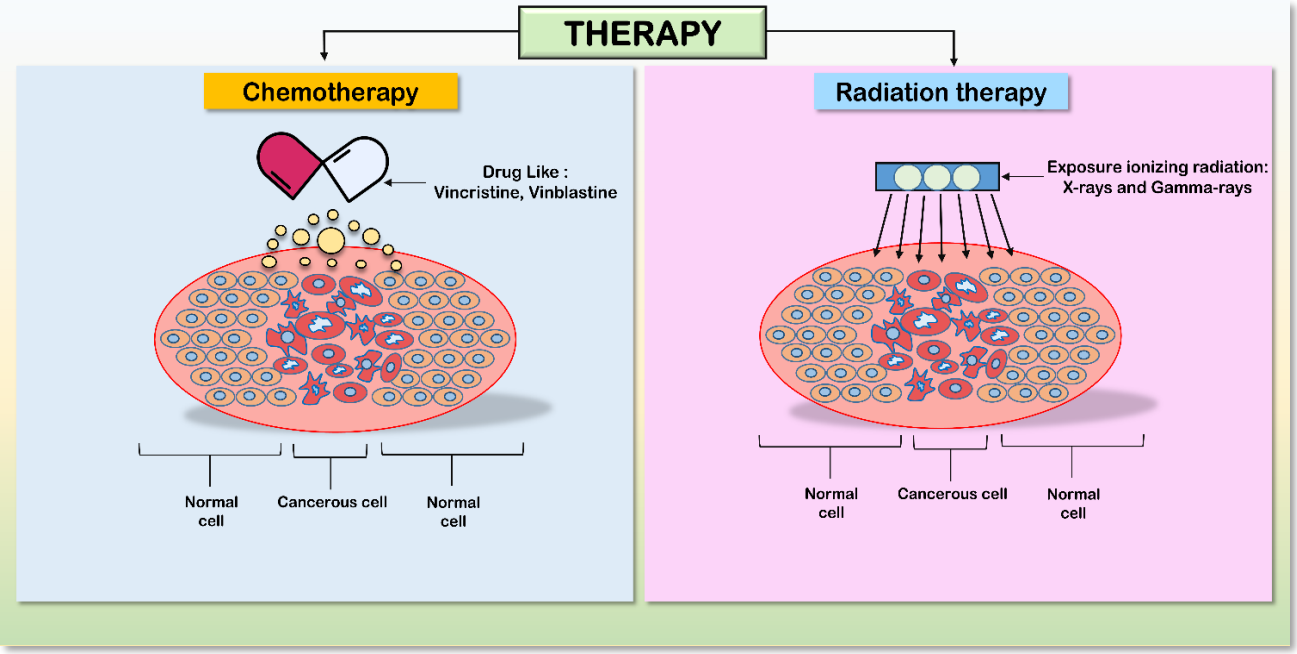

Figure 1: Depicts the conventional cancer therapies: Chemotherapy, which involves cytotoxic drugs, and radiation therapy, which uses ionizing radiation. While effective, both methods can also damage surrounding normal cells.

3.1 Targeted drug delivery

Using specialised drugs or delivery methods made to concentrate on specific body tissues or cells is known as targeted drug delivery thereby increase treatment efficiency. A promising method for delivering medications to certain locations, like tumours, while reducing systemic side effects is the use of MRI in targeted drug delivery. Because of its many benefits, such as increased drug solubility, higher bioavailability, and accurate targeting of damaged tissues, nanoparticles have become crucial parts of targeted drug delivery systems. These nanoparticles can be made to transport medications and directed to the desired location by attaching ligands that bind to particular target cell receptors or by applying external stimuli like magnetic fields (Yan et al., 2024). The development of multifunctional nanoparticles with properties like fluorescence, superparamagnetism, and pH responsiveness has opened up new avenues for imaging and targeted medication delivery. These developments have made it possible to create nanoparticles that can deliver medications to specific locations while also allowing for real-time tracking of their dispersion throughout the body (Liew et al., 2025).

3.2 Hyperthermia therapy

MRI-based hyperthermia therapy uses magnetic nanoparticles to provide localised heating, especially for targeted cancer treatments. One intriguing technique for improving targeted cancer treatment is to activate these nanoparticles using an external alternating magnetic field (Fatima et al., 2021). As a non-invasive cancer treatment that uses magnetic fields to destroy cancer cells, magnetic hyperthermia has gained attention as a helpful therapeutic approach for the treatment of malignant tumours (Mj, 2024).

3.3 Radiation therapy

High-energy radiation is applied during radiation treatment (RT) in order to target and kill cancer cells or shrink tumours (Zameer et al., 2025). MRI-guided radiotherapy systems have been crucial, offering special imaging advantages that improve treatment planning accuracy (Otazo et al., 2021). In order to precisely define the gross tumour volume and organs at risk (OAR) during RT planning and improve clinical outcomes for a variety of cancer types, MRI's outstanding soft-tissue contrast is essential. For a variety of malignancies, such as prostate neoplasms, lung neoplasms, brain neoplasms, and uterine cervical neoplasms, the use of MRI in RT planning has produced encouraging outcomes (Ladbury et al., 2023).

3.4 Immunotherapy

Immunotherapy is the use of the immune system to treat illnesses, usually by boosting or activating the body's defences against cancer or infections. The slow process of immune system activation against cancer cells depends on the precise localisation of tumours and the tracking of therapeutic responses made possible by MRI's high-resolution soft tissue imaging capabilities (Lau et al., 2022). The ability

to direct minimally invasive procedures further improves this precision by guaranteeing the accurate administration of immunotherapeutic drugs to the tumour location and minimising systemic side effects (Jiang et al., 2024).

3.5 Gene therapy

Gene therapy is a medical procedure used to treat or prevent tumour disorders by changing or replacing damaged genes. By enabling accurate and real-time gene delivery monitoring, MRI-guided gene therapy has improved target coverage efficiency and optimised surgical deployment. Monitoring the dispersion of viral vectors used for gene delivery is one important usage, as it enables real-time evaluation of the vectors' efficiency in reaching their target tissues (Sudhakar & Richardson, 2019). Additionally, MRI has been used to transport genes to the brain by injecting viral vectors intravenously. Transcranial focused ultrasound has been used to temporarily break the blood-brain barrier. Specialised nanoparticles, such as those based on dendrimers and copolymers, have been developed as a result of MRI integration with the goal of enhancing targeting efficiency in gene delivery systems (Bermudez et al., 2025).

4. Functionalization and Targeted imaging

Functionalization of nanoparticles refers to the chemical modification of their surface to improve biocompatibility, circulation time, and targeting capabilities. In the context of MRI contrast agents, surface functionalization enables the attachment of targeting ligands such as antibodies, peptides, aptamers, or small molecules that specifically bind to biomarkers expressed on diseased tissues, such as tumor cells (Avasthi et al., 2020). This targeted approach enhances the accumulation of nanoparticles at the site of interest, thereby increasing the local contrast and improving the sensitivity and specificity of MRI imaging. Superparamagnetic iron oxide nanoparticles (SPIONs), manganese-based, and gadolinium-based nanoparticles are commonly used MRI contrast agents that benefit from surface modifications (Vangijzegem et al., 2023). Functionalization with polyethylene glycol (PEG), for example, reduces opsonization and prolongs circulation, while conjugation with ligands like folic acid or RGD peptides promotes receptor-mediated uptake by cancer cells. This targeted imaging approach not only allows early detection of tumors and metastases but also aids in monitoring therapeutic response (Javid et al., 2024). The process of functionalization and targeted imaging as given in **Figure 2.**

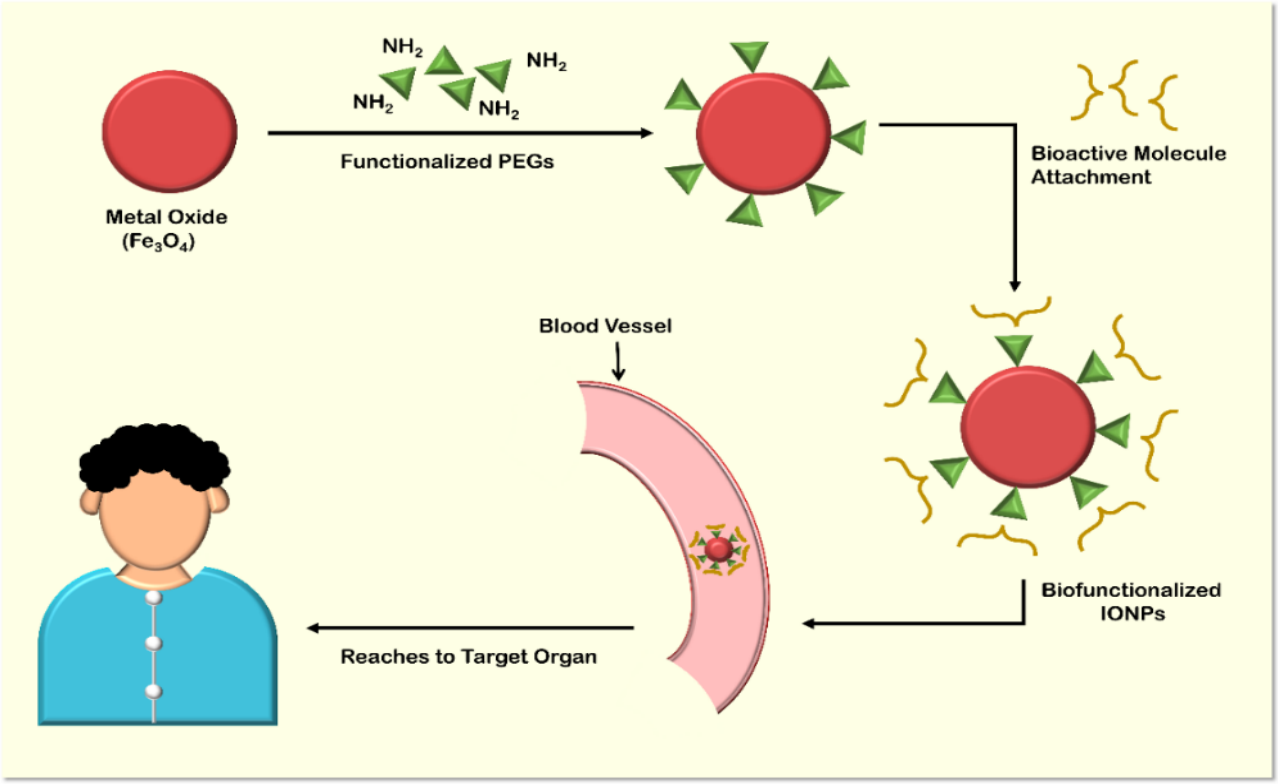

Figure 2: Schematic representation of functionalization and targeted imaging of nanoparticles used as MRI contrast agents. The nanoparticle core (iron oxide) is coated with a biocompatible polymer such as polyethylene glycol (PEG) to enhance stability and circulation time. Bioactive molecule or targeting ligands attached with nanoparticle surface to facilitate specific binding to receptors. Upon systemic administration, the functionalized nanoparticles circulate in the bloodstream and preferentially accumulate at the disease site through active targeting, enhancing MRI contrast at the target tissue and enabling precise diagnosis and monitoring.

4.1 Polymeric Coating

Surface coatings are an essential part of every Magnetic nanoparticle (MNP) platform for biomedical applications. The high surface energy, allow them to clump together even if they are not magnetically attracted because of their superparamagnetic characteristics (Ullah Khan et al., 2021). Colloidal electrostatic stabilization, which is caused by the repulsion of surface charges on the nanoparticles, is typically insufficient to prevent aggregation in biological fluids due to the presence of salts or other electrolytes that may neutralize this charge. Additionally, as the initial stage of the RES's clearance of MNPs upon intravenous injection, their surfaces undergo opsonisation, or the adsorption of plasma protein (Portilla et al., 2022). MNP applications in medicine is avoiding RES absorption while preserving a lengthy plasma half-life. To stop nanoparticle agglomeration and opsonisation, polymeric coatings offer a steric barrier. Furthermore, these coatings offer a way to customise MNPs' surface characteristics, including chemical activity and surface charge (Binandeh et al., 2021). The nature of the polymer's chemical structure (e.g., hydrophilicity/hydrophobicity, biodegradation characteristics, etc.), its length or molecular weight, how it is anchored or attached (e.g., electrostatic or covalent bonding), its conformation, and the extent of particle surface coverage are some crucial factors related to polymeric coatings that may have an impact on an MNP system's performance. Due to their long shelf life, poly (ethylene glycol) (PEG), poly(vinyl alcohol) (PVA), or natural polysaccharides (dextran and modified chitosan) are frequently employed coatings for MRI applications (Mannu et al., 2021).

4.2 Liposomes and Micelles -

One of the first applications of nanomedicine was the creation of liposomes as drug delivery systems. Liposome encapsulation provides the advantage of well-established in vivo behaviour, with long circulation durations due to processes like PEGylation. The capacity of liposomes to wrap several MNP cores and transport them collectively, without dilution, to a target location is another advantageous characteristic (Afzal et al., 2022). These delivery vehicles' versatility is further increased by including a medicinal substance in the payload. For similar purposes, MNPs have also been entrapped in multifunctional micelles made of amphiphilic block copolymers (Perumal et al., 2022).

4.3 Core-shell structures

Apart from organic coatings, core-shell structures that encapsulate the MNPs using biocompatible silica or gold have emerged as an appealing method for creating MRI contrast agents or MTCs for medication administration. These inert coverings, also known as shells, shield magnetic cores from chemical deterioration and stop potentially hazardous substances from escaping (Yang et al., 2020). Additionally, compared to materials that make up MNPs, functionalisation chemistries are typically more well-established with these materials. Because of their simplicity of synthesis and stability in aqueous environments, silica shells are appealing choices for protective coatings on MNPs (Willinger et al., 2021).

4.4 Functional ligands

Modular component addition to MNPs enables the combination or interchange of particular functional moieties and characteristics. These nanostructures can have ligands conjugated on their surface or integrated within them, including targeting agents, permeability enhancers, visual dyes, and medicinal compounds (Riaz et al., 2025). Protein coupling methods and bioconjugation chemistries have been researched to carry out such nanoscale engineering. It has been demonstrated that methods like avidin–biotin binding, the formation of amide, ester, or disulphide linkages using heterobifunctional linkers, and more recently, "click" chemistries, are effective in affixing functional ligands to MNPs (Stump, 2022). Combining organic dyes or fluorophores as optical imaging agents to enable detection by various imaging modalities is one example of giving MNPs additional functionality (Svechkarev & Mohs, 2019).

4.5 Passive targeting

Many MNP platforms are now able to take advantage of structural anomalies in the vasculature of specific disorders, including tumours, inflammatory sites, and infectious sites, thanks to the development of long-circulating nanoparticles. The mechanism behind this phenomenon, called the increase permeability and retention (EPR) effect, is that these tissues have "leaky" vasculature, which makes it easier for macromolecules and nanoparticles to extravasate and aggregate (Leporatti, 2022). Poorly structured vascular beds in tumours also lead to inadequate lymphatic drainage from these tissues. The RES's built-in clearance allows for passive targeting as well. These phagocytic cells, which are made up of tissue macrophages, blood monocytes, and bone marrow progenitors, absorb MNPs and use them to transport drug carriers and contrast agents to relevant organs (Wu, 2021).

4.6 Active targeting

The conjugation of targeting molecules with a high affinity for distinct molecular signatures present on malignant cells is a promising strategy for enhancing the local accumulation of MNPs in sick tissue. This technique is referred to as active targeting or selective targeting. These receptor-ligand or antigen-antibody interactions, which are frequently enhanced by the EPR effect, offer a useful tactic to lengthen the residency duration in cancerous cells like tumours (Long et al., 2025). Proteins, peptides, aptamers, and small molecules are examples of targeting ligands that have been studied to enhance the site-specific accumulation of MNPs. Specific binding may occasionally also make it easier for the nanoparticle to be internalised by receptor-mediated endocytosis (Yan et al., 2024).

4.7 Magnetic drug targeting (MDT)

The main drawback of the majority of chemotherapy drugs is their relative non-specificity, which increases the possibility of adverse effects on healthy tissues. In order to address this issue, MDT increases site-specific delivery of therapeutic medicines by using MNP carriers' attraction to an external magnetic field (Wang & Bai, 2023). A cytotoxic drug is typically attached to a biocompatible MNP carrier (also known as a magnetic targeted carrier, or MTC), which is then injected intravenously as a colloidal suspension. A magnetic field gradient is then applied to guide the MTC to the pathological site, and the therapeutic agent is released from the MTC. Additionally, it was demonstrated that patients tolerated these MTCs well (Veselov et al., 2022). Regrettably, a number of issues have been found with this technique, such as the potential for blood vessel embolization, the challenge of scaling up from animal models because commercial magnets have limited field penetration, the inability to control drug diffusion after release from the MTC, and toxic reactions to the MTCs. Only targets that were near the body's surface could be successfully targeted with MDT (Day et al., 2021).

5. Applications of nanoparticles-based contrast agents

5.1. Cancer imaging

MNPs have been thoroughly investigated as MRI contrast agents to enhance solid tumour identification, diagnosis, and treatment. Lesions as small as 2-3 mm can now be distinguished by clinical imaging of liver tumours and metastases using RES-mediated absorption of SPIOs (Tsilimigras et al., 2021). Furthermore, it has been demonstrated that USPIOs are useful in detecting lymph-node metastases with a diameter of 5-10mm under MRI. This non-invasive method has wide-ranging effects since identifying lymphatic spread is crucial for staging and choosing treatment strategies for conditions like colon, breast, and prostate cancers (Zhuang et al., 2021). Enhancing the delineation of brain tumour boundaries and quantifying tumour volumes is another clinical use of USPIO MNPs that are currently being evaluated. Diffusion of these tiny molecules from the tumour vasculature and the oedema surrounding the tumour are the usual limitations of current methods using gadolinium chelate-based contrast agents (Farinha et al., 2021). On the other hand, because of their slower removal from the tumour site and improved cellular internalisation, MNP-based contrast agents provide longer demarcation of tumour margins. These USPIOs have been found to be useful in differentiating between regions of radiation necrosis and neoplastic tissue, but they will not be able to replace gadolinium chelates (Hsu et al., 2023).

5.2. Cardiovascular disease imaging

For a number of clinical uses in cardiovascular medicine, such as myocardial damage, atherosclerosis, and other vascular diseases, MNPs have been suggested as MRI contrast agents (Salmanpour et al., 2024). These lesion-prone artery locations have also been visualised by taking advantage of the uptake of MNPs by macrophages, which have been demonstrated to be a marker of unstable atheromatous plaques (Fan et al., 2025).

6. Challenges and limitations

Before being used in clinical settings, some design aspects should be taken into account and further optimised, even though nano-based medicines have a lot of promise to produce rich imaging contrast. This entails guaranteeing large-scale, reproducible, and economical NP synthesis, optimising their imaging sensitivity, addressing issues with toxicity and biocompatibility, and facilitating efficient transport to target locations.NP deployment to the clinic is hampered by a few basic issues (Schneider-Futschik & Reyes-Ortega, 2021). The reticuloendothelial system (RES), which quickly transports NPs from the circulation to the liver, spleen, and bone marrow, is the first of these delivery barriers. Applying polyethylene glycol to the NP can lengthen circulation durations and decrease RES recognition of the NP. Because of their size, which hinders easy extravasation, nanoparticles are frequently only used in vascular applications. This RES accumulation frequently gives rise to worries about NP toxicity. Due to capillary blockage, aggregation may result in NP entrapment in the liver, lungs, or other organs, or in a loss of function. Circulation time is the last issue unique to theranostic NPs (Nowak-Jary & Machnicka, 2024). For imaging, the signal strength of the area of interest must be higher than that of the surrounding tissue in order to provide contrast. As a result, the majority of imaging agents are made to dissolve rapidly in the blood (for example, between a few minutes to several hours) (Lv et al., 2023). Longer circulation durations of NPs are necessary for both medication release and sufficient exposure to the tumour in a therapeutic approach. Oral bioavailability is the last difficulty. Switching to a less invasive method is crucial because the current NP design necessitates intravenous administration (Shan et al., 2017).

CONCLUSION

The contrast agent plays a significant role diagnosis. However, the conventions MRI contrast has certain limitations. Contrast imaging has evolved significantly after the use of nanoparticles-based MR contrast agents such as manganese-based nanoparticles (MnO), and iron-oxide-based nanoparticles (SPIONS). They have higher efficiency and accuracy in diagnostic procedures. They can me made specially for a particular disease allowing personalized and target imaging, involving greater selectivity for diseased tissues, especially in cancer, longer circulation, and enhanced contrast by functionalization and active targeting. The combination of therapeutic and diagnostic properties makes nanoparticles even more potent instruments for precision and individualized therapy. Apart from the clinical potential of MRI contrast agents based on

nanoparticles, despite the fact that safety, scalability, and regulatory approval concerns still a challenge. Nanoparticles have the potential to fundamentally alter the field of targeted diagnostics and non-invasive imaging as it advances.

Consent and ethical approval

Not required

Competing interests

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